

Appl. No.10/085,612
Reply dated March 8, 2004
Reply to Office Action mailed October 8, 2003

Remarks/Arguments

Amendments to the Specification

The title is amended to be descriptive of the elected invention as requested in the Office Action.

The reference sentence describing the relationship of this application to one of the priority applications is amended to indicate its current status as an issued US patent.

Trademarks used in the specification as noted in the Office Action are now capitalized and include the symbol TM or ®, as appropriate, to denote their status as a trademark.

Amendments to the Sequence Listing

All nucleic acid sequences in the disclosure are included in the substitute Sequence Listing submitted as a paper copy herewith. The required CRF was submitted electronically using EPAVE 5.1 this morning, as documented with the attached submission Acknowledgement Receipt. A statement asserting that the attached paper copy and the electronically submitted CRF of the Substitute Sequence Listing are identical, and include no new matter, is attached hereto.

Each disclosed sequence was identified by a SEQ ID NO. in the application as filed, however two different sequences were identified in the application as SEQ ID NOS:23 and 24. An amendment to the specification is made herein to eliminate this duplication. The amendment requests that the sequence in Table 9 on p. 34 of the application designated as SEQ ID NO:23 be changed to SEQ ID NO:27 and the sequence in Table 9 designated as SEQ ID NO:24 be changed to SEQ ID NO:28..

Amendments to the Claims

Claims 19-21, 23, 24, and 27-34 are canceled.

Claim 17 is amended to clarify the language and to direct the claim to screening an individual for predisposition for reduced metabolism of a CYP3A4 or CYP3A5 substrate. Support for this amendment is found in the claim as filed and in the specification at p. 8, lines 18-21; p. 14, lines 12-13, p. 29, lines 11-12 and p.32, lines 4-6.

New Claim 35, depending from amended claim 17, is added. Support for this new claim is found in the specification at p. 15, lines 25-29; p. 28, lines 6-20 and at p. 31, lines 2-12.

Claim 18 depending from amended claim 17 is amended to provide consistent language

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with the independent claim. Support for this amendment is found in claims 17 and 18 as filed.

Claim 22, depending from amended claim 17, is also amended to provide consistent language with the independent claim and to clarify the claimed substrate. New dependent claims 36-38 further define the claimed substrates. Support for these amendments is found in claims 17, 22-23 as filed and at p. 3, lines 1-6; p. 4 lines 24-27; and p. 11, lines 8-10.

Claim 25 is amended to clarify the language of the claim. Support for this amendment is found in the claim as filed and in the specification at p. 14, lines 12-13; p. 22, line 26 to p. 23, line 5; p. 30 lines 14-20, p. 33, lines 2-10; and p. 36, lines 14-19.

Claim 26, depending from claim 25, is amended to provide consistent language with the amended independent claim. Support for this amendment is found in claims 25 and 26 as filed.

New claims 39-44, depending from claim 25, are added. Support for these new claims is found in claims 25 and 30 as filed and in the specification at p. 4, lines 24-27; p. 5 line 8 and lines 19-20; p. 14, lines 27-28; p. 15, lines 25-29; p. 28, lines 6-20 and at p. 31, lines 2-12, p. 33, lines 15-p. 34, line 13.

Applicants respectfully submit that the new claims are directed to the elected subject matter, and thus their entry for substantive examination is warranted.

Applicants believe that no fees for additional claims are due. However if that is incorrect, Applicants note that they qualify as a small entity and hereby authorize you to debit deposit account 50-1293.

Priority

The Office Action accorded the effective filing date of the instant claims as the filing date of the instant application (February 26, 2002) stating that neither the 09/144,367 application nor the 60/271,630 application disclose the CYP3A5 or the GSTM1 mutations recited in the instant claims and also that neither application provide evidence that any of the recited polymorphisms are associated with reduced substrate metabolism.

Applicants assert that the effective filing date of the instant claims is earlier than the filing date of the instant application. The claims of the instant application appeared in application 60/271,630, on pages 37-46 of the specification, with elected claims 17-34 appearing on pp. 41-46. In fact, application 60/271,630 appears to Applicants' Agent to be substantially identical to the instant application throughout its entirety, pp. 1-47. Additionally, the present application claims priority to application 09/144,367. Applicants assert that the discovery and detection of the

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CYP3A4 polymorphism was disclosed in application 09/144,367, now issued as US patent 6,432,639 (See col. 10, line 28 to Col 12, line 37, and Tables 1-3). Consequently, Applicants request reconsideration and revision of the effective filing date accorded the instant claims.

Rejections Under 35 USC §112

Claims 25-34 were rejected under 35 USC §112, first paragraph, for lack of enablement for methods in which CY and BCNU are not selected when the GSTM1 null mutation is present. Claims 25 and 26 are herein amended and new claims 39-43 are added to reflect the observations reported in the example for the association of the GSTM1 null mutation with patient outcomes. Claims 27-34 are canceled. Thus, Applicants believe that amended claims 25 and 26 now meet the enablement requirement of §112, first paragraph and request reconsideration and withdrawal of these rejections.

In the Office Action, Claims 17-34 were rejected under 35 USC §112, second paragraph, as being indefinite and failing to particularly point out and distinctly claim the subject matter of the invention.

The Office Action stated that claims 17-24 were indefinite over recitation of the language "detecting the presence or absence in said individual of a polymorphism..." in claim 17 by failing to relate the two steps to each other, or to the claim objective. Claim 17 is amended herein to clarify the relationship of the steps to each other and to the objective of the method. Claims 18 and 22 are each amended to be consistent with the language in independent amended claim 17, thereby eliminating the antecedent basis problem in claim 18 noted in the Office Action. Claims 19-21, 23 and 24 are canceled.

The Office Action stated that claims 25-29 were rejected as being indefinite over use in claim 25 of "said individual" without sufficient antecedent basis, lack of clarity in claim 25 as to how the two steps are related and the language in claim 25 of the selecting step. Claim 25 is amended herein to eliminate the lack of antecedent basis, to clarify the language of the selecting step and to clarify the relationship between the steps. Claim 26 is amended to be consistent with the language in amended independent claim 25, thereby eliminating the antecedent basis problem in the claim noted in the Office Action. Claims 27-29 are canceled.

The Office Action stated that claims 30-34 were rejected as being indefinite over use in claim 30 of "said individual" without sufficient antecedent basis, and for lack of clarity in claim 30 as to how the two steps are related. New claim 44, depending from amended claim 25, is now

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directed to the subject matter of original claim 30. Thus, claims 30-34 are canceled.

For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of all rejections of amended claims 17, 18, 22, 25, and 26 under 35 U.S.C. §112.

Rejections Under 35 USC §102

For a claim to be anticipated under 35 U.S.C. §102, a single reference must teach every element of the claim. (*Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379.).

The Office Action states that claims 17-19, 21 and 24 are anticipated by Rebbeck et al. (US 6,174,684, issued January 16, 2001) under §102(b). The Office Action states that Rebbeck et al. disclose and exemplify obtaining DNA samples including the CYP3A4 gene from cancer patients and that Rebbeck et al. meet the requirements of claim 17 by teaching a step of detecting the presence or absence in said samples of the CYP3A4 A to G polymorphism located at position -392 relative to the CYP3A4 start codon, since the ability of a particular polymorphism to affect metabolism is inherent to it. The Office Action further states that regarding claim 18, Rebbeck et al. disclose determination of whether individuals are homozygous or heterozygous for the CYP3A4 polymorphism; regarding claim 19, Rebbeck et al. disclose a genomic DNA assay; and regarding claim 21, Rebbeck et al. disclose detection by amplifying a region of CYP3A4. Further, the Office Action notes that regarding claim 24, the manner in which a polymorphism affects metabolism of various substrates is inherent to the polymorphism. Applicants note that claim 24 is drawn to a method involving only the GSTM1 null mutation, and presume that the Office Action meant to reject claim 22, drawn to a method involving CYP3A4.

Amended claims 17, 18, 22 and new claims 35-38 are now directed to a method of screening an individual for predisposition for reduced metabolism of a CYP3A4 substrate or a CYP3A5 substrate. Claims 19-21 and 24 are canceled. As Rebbeck et al. did not disclose detecting this CYP3A4 polymorphism in order to determine if an individual is predisposed to reduced CYP3A4 substrate metabolism, Rebbeck et al. do not anticipate amended claims 17, 18, 22 and new claims 35-38.

Moreover, Applicants note that the CYP3A4 polymorphism comprising a G at position -392 of the promoter of the CYP3A4 gene with respect to the start codon and methods of detecting it in individuals were disclosed in application 09/144,367 (issued as US 6,432,639), filed August 31, 1998, to which the instant application claims priority as a continuation-in-part (See entire reference, particularly col. 10, line 28 to Col 12, line 37, and Tables 1-3). As the filing date of

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09/144,367 is earlier than the publication date (Jan. 16, 2001) of the Rebbeck et al patent, the Rebbeck et al. patent is not prior art under §102(b).

The Office Action rejects claims 17-21 and 24 under 35 USC §102(b) as being anticipated by Van Schaik et al. (2000). Applicants noted above that claim 24 is drawn to a method involving only the GSTM1 null mutation, and presume that the Office Action meant to reject claim 22, drawn to a method involving CYP3A4.

As noted previously, claims 19-21 and 24 are canceled, while amended claims 17, 18, 22 and new claims 35-38 are directed to a method of screening an individual for predisposition for reduced metabolism of a CYP3A4 substrate or a CYP3A5 substrate. As Van Schaik et al. do not disclose detecting this CYP3A4 polymorphism in order to determine if an individual is predisposed to reduced CYP3A4 substrate metabolism, Van Shaik et al. do not anticipate amended claims 17, 18, 22 and new claims 35-38.

Additionally, Applicants note that Volume 11 of Clinical Chemistry in which the Van Shaik et al. article appears is dated November 1, 2000, according to the journal's website. Applicants believe, as argued above in the section entitled **Priority**, that the effective filing date of the claims in the instant application is no later than February 26, 2001, the date of filing the provisional application 60/271,630. As November 2000 is less than one year prior to February 26, 2001, Van Shaik et al. is not prior art under 35 USC §102(b).

Further, as noted above in discussing the Rebbeck et al. reference, this polymorphism and methods of detecting it in individuals were disclosed in application 09/144,367 (issued as US 6,432,639), filed August 31, 1998, to which the instant application claims priority as a continuation-in-part (See entire reference, particularly col. 10, line 28 to Col 12, line 37). The disclosure in this priority document is earlier than the publication date (2000) of the Van Shaik et al article, therefore the Van Shaik et al. publication is not prior art under §102.

The Office Action rejects claims 17-19 and 24 under 35 USC §102(a) as being anticipated by Petros et al. (March 2001). Applicants believe, as argued above in the section entitled **Priority**, that the effective filing date of these claims in the instant application is no later than February 26, 2001, the date of filing the provisional application 60/271,630. The abstract of Petros et al. was published subsequent to filing application 60/271,630, therefore Petros et al. is not prior art under §102.

The Office Action rejects claims 17-19, 21 and 24 under 35 USC §102(a) as being anticipated by Ambrosone et al. (October 2001). Applicants believe, as argued above in the section

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on **Priority**, that the effective filing date of these claims in the instant application is no later than February 26, 2001, the date of filing the provisional application 60/271,630. The publication of Ambrosone et al. was published subsequent to filing application 60/271,630; therefore, Ambrosone et al. is not prior art under §102.

For the foregoing reasons, Applicants request reconsideration and withdrawal of all rejections of amended claims 17, 18, and 22 under §102.

Rejections Under 35 USC §103

The Office Action rejects claim 21 under 35 USC §103(a) as being unpatentable over Petros et al. (March 2001) in view of Ambrosone et al. (October 2001).

As discussed above, Applicants believe that the effective filing date of claim 21 in the instant application is no later than February 26, 2001, the filing date of the provisional application 60/271,630. The publications of Petros et al and Ambrosone et al. were each published subsequent to February 26, 2001 and therefore neither publication qualifies as *prior* art. Thus, the Office Action has failed to establish a *prima facie* case of obviousness under §103(a).

37 CFR 1.56 Disclosures

In accordance with the obligation to disclose information material to patentability under 37 CFR 1.56, Applicants note that inventions disclosed in application 09/144,367, from which the instant application is a continuation in part, were owned solely by PPGx at the time they were made, which was prior to the joint invention by the six named inventors of the subject matter of the pending claims. The pending claims were co-owned by PPGx and Duke University at the time of their invention.

Summary of Interview of February 24, 2004

Applicants' Agent thanks the examiner for making the time for the telephonic interview on 24 February 2004. The Interview Summary Form sent by the examiner is consistent with the content of the discussion in the interview.

In brief, draft language of independent claims 17 and 25 was discussed with respect to §112, first and second paragraphs. The priority claim to provisional 60/271,630 and the effect of that priority claim on the effective filing date of the elected subject matter was also discussed. In particular, the examiner agreed that the 60/271,630 application appears to provide basis for the

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claimed invention. The examiner stated that the next Office Action would be made non-final if the examiner's error with respect to the priority to the 60/271,630 application necessitated new and/or modified rejections. Additionally, the examiner noted that the application appeared to contain allowable subject matter.

Should any questions arise, or if Applicants or Applicants' Agent can facilitate examination of this application, it is respectfully requested that the undersigned Agent be contacted so that any remaining issues can be resolved.

Respectfully submitted,

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